Breast cancer, human immunodeficiency virus and highly active antiretroviral treatment; implications for a high-rate seropositive region

Subash Chirkut

King Edward VIII Hospital, Durban; Department of General Surgery, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal (UKZN), South Africa

Abstract

Sub-Saharan Africa is the region in the world with the most people infected with the human immunodeficiency virus (HIV). The incidence of breast cancer is also rising in the region. This transcript focusses on the burden of these two diseases when they converge in the same populace. This comprehensive literature review of the topic suggests a trend towards an increasing incidence of breast cancer in the HIV-infected population, and the rationale for such a tendency is hypothesized, especially in the context of the availability of highly active antiretroviral therapy. Besides the age at diagnosis, all other clinical characteristics appear to be similar in HIV-positive and HIV-negative breast cancer populations. Outcomes of the different treatment modalities for breast cancer in HIV-positive patients are also appraised and finally innovative areas of future research are suggested along with plausible recommendations.

Introduction

Globally, the majority of people living with HIV and AIDS (PLWHA) reside in Sub-Saharan Africa (SSA).[1] Women comprise 53% of the estimated 4 million HIV-infected adults living in South Africa.[2] Worldwide, the life expectancy of HIV-infected individuals has increased with the introduction of highly active antiretroviral therapy (HAART) which coincides with a dramatic decrease the incidence of opportunistic infections and AIDS-defining cancers (ADC).[3]

Correspondence: Subash Chirkut, King Edward VIII Hospital, Durban; Department of General Surgery, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal (UKZN), Private Bag X7, Congella Durban 4013, South Africa.
Tel.: +27826999226.
E-mail: chirkut@ukzn.ac.za

Key words: Breast cancer; HIV; HAART; chemotherapy; Sub-Saharan Africa.

Received for publication: 25 May 2018.
Revision received: 2 October 2018.
Accepted for publication: 3 January 2019.

Oncology Reviews 2019; 13:376
doi:10.4081/oncol.2019.376

The incidence of breast cancer (BC) is however increasing in SSA[4,5] and has since 1995 overtook invasive cervical cancer (ICC) as the leading cause of cancer in South African women.[6] The coexistence of these two diseases in a patient has become a reality,[7,8] which significantly affect health in women.[9]

This narrative review focuses on BC in PLWHA with particular reference to: epidemiology, treatment outcomes and future areas of research. The evidence presented will be interpreted in the context of three historical time frames: pre-HAART, early HAART and HAART. While BC does occur in men living with HIV/AIDS (MLWHA),[10] this review will mainly focus on BC in women living with HIV/AIDS (WLWHA). Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) that may also have localized to the breast in PLWHA,[11-13] falls outside the scope of this review.

Incidence of breast cancer in people living with HIV and AIDS

The first case of BC in an HIV-infected person was reported in the literature in 1988[11,14] and only 42 detailed patient reports were available until the early 2000s.[15] While two relatively small cohorts[3,16] reported a marginal increased incidence in BC in WLWHA; the vast majority document a statistically significant deficit.[17,18] Amir and colleagues' evaluation of the Tanzanian Cancer Registry (1966 to 1996) showed a statistically significant decrease in the incidence rate of BC in both males (P=0.001) and females (P=0.021) after 1982, coinciding with the appearance of HIV/AIDS.[19,20]

Standardized incidence ratio (SIR) is the ratio of the rate of observed cancer incidence in a sample population, compared to the cancer incidence expected for the general population. A value of 1 will indicate the same incidence rate and less than 1 indicating fewer cancers occurring than expected. The SIR for the incident BC among WLWHA in *Women's interagency HIV study (WIHS)* was 0.7.[21] Other cohorts have shown the equivalent.[17]

Matching population based cancer registries with HIV/AIDS registries may provide the best level of evidence to verify this trend.[22] Using this method, the majority of studies have shown a significantly lower SIRs for BC in WLWHA.[23-27] A meta-analysis of 18 studies, from high-income countries (HIC) published mainly in the pre- and early HAART period, showed a lower incidence of BC in PLWHA than compared to the general population (SIR 0.74, 95% Confidence Interval (CI) [0.56-0.97]).[28] However, this seemingly changed with introduction of HAART in the mid-1990s and its increased availability in early 2000s.

More recent and updated cohort studies have clearly shown a shift towards increasing SIR,[26,28-33] approaching that of the general population.[34] In a contemporary report of 151 HIV-infected BC patients in Soweto, South Africa, which constitutes the largest

cohort to date, Cubasch *et al.* reported an equal prevalence of HIV in BC patients compared to women in the source population (RR 1.20, P=0.13).[5]

Hypothesis for the decreased incidence of BC in PLWHA

Under-reporting and competing mortalities

Published case reports are likely to select patients in whom the outcome was poor, and include only a small fraction of individuals in whom both HIV infection and BC has been diagnosed.[35] BC is rarely explored and recognized in WLWHA[36] and asymptomatic HIV infection is under-recognized in cancer patients.[37] Underreporting of cancer cases in SSA countries is confounded by several reasons such as the use of alternative remedies, systemic failure in referrals, and economic difficulty.[20] Added to this, there are few reliable population-based national cancer registries, and the information available is gleaned from individual units in the larger healthcare centres.[38-40]

In the pre-HAART period, PLWHA may have succumbed to other illnesses before the development of BC.[9]

Traditional BC risk factors

The apparent deficit of BC among females in the WIHS was explained by a general overall lower risk of established BC risk factors: lower social class, early age at first childbirth, high parity, and low alcohol intake.[21] The endogenous estrogen microenvironment contributes to the proliferation of breast tissue and is an important prognostic factor. Lower estrogen levels may place BC cells at a survival disadvantage and decrease their malignant potential. Early in the HIV/AIDS epidemic estrogen levels have been reported to be lower in HIV-infected premenopausal women compared to HIV-uninfected controls.[34,41]

Immunosuppression

It is not clear what role immunosuppression may play in the pathogenesis of BC.[42] One is also not able to eliminate the possibility that immunodeficiency may protect PLWHA from developing BC.[43,44]

Analyses of cancer incidence in chronically immunosuppressed transplant recipients have demonstrated a similar unexpected low incidence of BC relative to other malignancies.[43,45] Grulich *et al.* examined seven studies of people with HIV/AIDS (n=44,172) and five of transplant recipients (n=31,977). For 20 of the 28 types of cancer examined, there was a significantly increased incidence in both populations. Rates for BC was no different from population rates in both groups, thus suggesting that immune deficiency due to organ transplant or HIV does not increase the risk of BC.[46]

Some investigators have speculated that a normal immune response maybe needed to facilitate BC development, and HIV immunosuppression may thus be protective against BC.[15]

HIV virus

HIV may directly and indirectly affect the glandular, mesenchymal, and intra-mammary lymphoid tissue in seropositive patients.[11] *In vitro* studies suggest that HIV replication in human breast cells hinders their growth by affecting growth factor receptors, suggesting that HIV infection may counteract oncogenesis in BC cells.[47,48] While HIV may infect breast tissue, its main target is T lymphocytes with cluster differentiation 4 (CD4) receptors on its surface. HIV-1 uses CD4 and a chemokine receptor for cellular entry. After the binding of the HIV-1 envelope glycoprotein (Env) gp120 to CD4, gp120 changes its conformation to bind to a chemokine receptors and initiates fusion with the cellular membrane. The chemokine receptors CCR5 and CXCR4 are the main co-receptors for the cellular entry of HIV-1. In general, viral strains are classified into R5, X4 and R5X4 according to the usage of chemokine receptor.[49]

CXCR4 has recently been shown to be expressed not only on immune cells, but on primary tumours of human invasive lobular or ductal breast carcinoma and to mediate organ-specific metastasis.[49,50] Thus, it seems that CXCR4-using variants of HIV preferentially infect (and terminate) BC cell lines that express CXCR4. The low BC risk with HIV have been reported to be specifically linked to CXCR4-using variants of HIV.[50]

Hypotheses for the increasing incidence of BC in PLWHA

Aging

With HAART now being widely available in most of SSA and in HIC, PLWHA are living longer. The increase in incidence of non-AIDS-defining cancers (NADC) in PLWHA has mainly been driven by growth and aging of the AIDS population[29,51] and as WLWHA get older, the incidence of BC is likely going to increase.[52,53]

Additionally, HAART has been shown to enhance events seen in biological aging - that is to say HAART accelerates the aging process.[54,55]

Comorbidities and HAART

Metabolic syndrome (MS) has been shown to be more prevalent in BC patients and is an independent risk factor for BC. MS consists of a constellation of metabolic abnormalities which include central obesity, hyperglycemia, hyperinsulinemia, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, hyperuricemia, and increased levels of fibrinogen. It confers an increased risk of cardiovascular disease and diabetes mellitus.[56,57] The prevalence of MS among HAART-exposed PLWHA has been shown to be significantly higher compared to HAART-naïve PLWHA.[58] Several published studies found an overall increase in the incidence of MS in patients with HIV receiving HAART over time, making this comorbidity particularly relevant for PLWHA and BC.[48] It seems that HAART prevents the wasting syndrome of AIDS (common in the pre-HAART period)[34] which may increase endogenous estrogen levels.[41] During the HAART period it has been shown that WLWHA in the USA tended to have significantly higher body mass index(BMI),[34] an established risk factor for BC development.[59]

Finally, if the deficit in BC reflects the ability of HIV to infect, replicate in, and impair proliferation of breast cells, then HAART would likely reduce HIV replication and perhaps allow cancer cell proliferation, either directly or indirectly.[34]

With regard to individual antiretroviral agents, studies have demonstrated that *efavirenz* directly binds and activates estrogen receptors in breast tissue, providing a plausible mechanistic explanation for *efavirenz*-induced gynecomastia in PLWHA and may encourage BC development.[60]

HAART as a carcinogen

The carcinogenic potential of individual drugs in the HAART regimen may itself be a possible risk factor for malignancy. Though there have been some reports of an association between some antiretroviral agents and the occurrence of cancer,[61,62] a correlation has not been confirmed.[63] Pharmaceutical companies have nevertheless listed this as a possibility in the prescribing information for some antiretroviral drugs.[64]

Other viruses

The role of a preexisting viral infection in the pathogenesis of BC has been suggested[11,19] but at present unproven.[65] However, an animal model exists to demonstrate this conjecture. The mouse mammary tumour virus (MMTV) is a retrovirus that can infect mice and it is known to cause the majority of murine mammary tumours.[66,67] Human herpesvirus 8-induced KS and Epstein-Barr virus-induced NHL are ADCs and are associated with a low CD4 count. With immune reconstitution as a result of HAART, their incidence has declined in PLWHA. The association between Human papillomavirus (HPV)-induced ICC and low CD4 is tentative.[68] With the availability of HAART, an increased incidence of other viral-related non-AIDS-defining cancers (NADC) have emerged in PLWHA. These include Hepatitis B-induced Hepatocellular carcinoma and HPV-induced genitourinary,[69] anal,[70] conjunctival,[71] head and neck cancers.[55] These cancers are not associated with a low CD4 count. In contrast to ADC, HAART has had little impact on the incidence of NADC.[72] If BC does have a viral association then, with immune reconstitution, its incidence may increase with time.

Reconciling the hypotheses

BC develops as a result of the complex interplay of host, genetic, metabolic, immunologic, and environmental factors,[8,48] and with the evolution of HIV/AIDS epidemic, factors abetting BC pathogenesis may have emerged, mainly driven by the availability of HAART.

Clinical and pathological characteristics of BC in PLWHA

Age at presentation

Case reports, case series and cohorts from the HIC and low-to-middle-income countries (LMIC) have consistently demonstrated that BC occurs at a younger age in PLWHA.[3,41,53,73,74] A 2-year study at the Tygerberg Academic Hospital in Cape Town, South Africa, reported similar tendencies, with a median age at presentation of 54 years for patients without HIV compared with 42 years for patients with HIV (P=0.001).[75] This finding has been confirmed by other SSA studies.[5,7,76,77]

Some studies noted a great proportion of patients with a family history of breast or ovarian cancer, suggesting a possible influence of HIV on acceleration of oncogenesis and increased penetrance in patients who may already have a heritable risk.[78]

In general, the age at diagnosis for most cancers in PLWHA is ~20 years younger than their general population.[71,79]

CD4 count at presentation

The vast majority of case series and cohorts have shown little or no association between CD4 count and the development of BC.[5,34,53,59,73,74,80-82] In *the ONCOVIH study* (France), consisting of 21 BCs in WLWHA, the median CD4 cell count was 347 cells/mm^3 (range: 180-1039),[51] while in Durban, South Africa the median CD4 count was 435 cells/mm^3 (range 80-945).[77] BC in WLWHA is certainly not associated with a low CD4 count[34] implying that the degree of immune-compromise does not correlated with tumorigenesis.[82]

CD4 count is also not associated with BC stage at presentation, histological subtypes, or tumor grade.[48]

Stage of presentation, pathology and grade

Early in the HIV epidemic many authors perceived that BC, *in the setting of HIV infection, tends to occur at a relatively early age, usually with increased bilateral disease, unusual histology and early metastatic spread, resulting in a poor outcome and early relapse*.[10,19,36,41,83,84] Over time, as more data appeared in the literature, this statement has been refuted.[85,73] In their updated case series from Harlem, New York, *Sarhan and Oluwole* demonstrated that the cancer stage, pathological cancer characteristics and survival outcome was similar in HIV-positive and HIV-negative patients.[9] More recent legitimately credible studies from SSA also demonstrated no statistically significant difference in the stage at presentation, histologic subtype, tumor grade, or nodal involvement between HIV-positive groups and the other groups.[7,75,77,86]

BC treatment and its outcome in PLWHA

Surgery, radiotherapy, hormonal therapy, and chemotherapy are the most common means of treatment for BC patients.[59]

Surgery

Current literature suggests that healthier patients with HIV infection, on HAART, have better surgical outcomes,[87] and that HIV infection is not associated with increased in-hospital mortality.[88] In the only study that looked specifically at surgery in HIV-infected women with BC Phakathi *et al*. discovered that HIV-infected patients did not experience more surgical complications than the non-infected patients. Rather, the risk ratio of HIV-infection for complications was 0.20, and the odds ratio 0.23, albeit with a wide 95% confidence interval (0.03 to 1.45).[7] The higher rate of surgical complications in the HIV-non-infected patients was explained by the fact that they were significantly older than the HIV-infected patients. This age difference was not unexpected as BC in PLWHA occurs at a younger age.[5,7]

Radiotherapy

Very little data is available regarding the use of radiotherapy in HIV-infected BC patients.[7] In a recent prospective study (n=160), 12 (86%) and 40 (98%) of HIV-infected and HIV-non-infected patients respectively completed their course of radiotherapy with no increase in acute infection, dermal or mucosal toxicity.[7] The available evidence suggests that patients with BC and HIV should be treated according to the guidelines for those who are immunocompetent.[89,90]

Hormone therapy

Tamoxifen is a selective estrogen receptor antagonist, and since its introduction in cancer therapy has become the standard treatment option for hormone-responsive BC patients.[91] Other drugs that are used to manipulate the hormone environment in BC patients include aromatase inhibitors (*e.g. anastrozole, exemestane*) and gonadotropin-releasing hormone analogues (*e.g. goserelin*).

In WLWHA with estrogen receptor-positive (ER+) BC, treatment with hormone therapy has no significant side effects, and is very well tolerated.[15,74,92]

Chemotherapy

Chemotherapeutic intervention remains a fundamental treatment strategy for the management of BC, either in the neoadjuvant or in adjuvant setting.

A few cases reports documented poor tolerance to chemotherapy while others demonstrated the contrary.[10,83,93,94] Case series from the pre-HAART[6,92] and early-HAART[37] period noted that chemotherapy was poorly tolerated by PLWHA. Besides significant toxicity from chemotherapy, chemotherapy resulted in progression of HIV disease.[82,95] HAART has been associated with better cancer outcomes as a result of maintaining reduced viral loads[53] and improved immunity.[96] This also seems to be the case for the treatment of BC in WLWHA.[76]

Of their 10 HIV-infected patients who received chemotherapy for BC, Singh e*t al.* observed that 60% completed adjuvant therapy, with 50% and 20% requiring treatment delay or dose reduction, respectively.[78]

In the era of HAART, Parameswaran *et al.* reported that their HIV-infected cohort (n=52) experienced chemotherapy with more adverse effects than the non-HIV-infected cohort (55% *vs* 30%; P=0.03), leading to more chemotherapy dose reductions and/or delays. Eighty four percent of HIV-infected patients were on HAART. The most common toxicities necessitating the dose reduction and/or delay were anemia and neutropenia (with or without fever).[81] They did not however find significant independent differences in outcome between HIV and non-HIV groups.

While anemia can easily be managed by a blood transfusion, neutropenia still remains a serious setback that can result in infection-related complications.[97]

More recently Nigidi *et al* narrated that patients with HIV infection were almost two times more likely to develop neutropenia than their HIV-negative counterparts (hazard ratio 1.76, [95% CI 1.06-2.92]; P=0.029).[77] Ninety five percent of patients were on HAART. It seems HAART did not prevent patients with HIV infection from experiencing neutropenia, but it did protect them from developing higher grades of neutropenia and more severe complications.[77]

Intriguingly, Langenhoven *et al.* reported no difference in the rate of neutropenia between HIV-infected patients and HIV-non-infected patients, however she did note an increase rate of lymphopenia (26%) in HIV-infected patients compared to HIV-non-infected patients (0%).[75] Eighty four percent of both HIV-positive and HIV-negative patients completed chemotherapy. All patients where receiving HAART.[75]

These toxicities seem to be unrelated to CD4 count [92] inferring that immuno-compromise and immune reconstitution does not sufficiently explain these findings, and that drug-drug interactions (DDI) may play a greater role than what was previously thought.[81]

Protease inhibitors (PI, *saquinavir, ritonavir, indinavir, fosamprenavir, lopinavir/ritonavir, atazanavir, darunavir, tipranavir*) are a class of drugs that are infamous for causing DDI due to their close relationship with the cytochrome P450 system (CYP 450). In particular, PIs inhibit the CYP3A4 enzyme and may reduce the hepatic metabolism of alkylating agents (e.g., *cyclophosphamide*), anthracyclines (e.g., *doxorubicin*), and taxanes (e.g., *paclitaxel*) that are used in the treatment for BC. The resulting increased levels of these cytotoxic agents may potentiate the risk for myelosuppression.[81,98] In contrast non-nucleoside reverse transcriptase inhibitors (NNRTI, *nevirapine* and *efavirenz*) are CYP3A4 inducers [51] and may reduce efficacy of these chemotherapeutic agents.

Zidovudine, a nucleoside reverse transcriptase Inhibitors (NRTIs) is known to cause serve bone marrow suppression, which maybe aggravated by chemotherapeutic drugs.[81,99] Interestingly, *zidovudine* was first synthesized in 1964 as a treatment for cancer but had little anticancer activity and unacceptable toxicity.[100] Nevertheless, in 1987 it was repurposed as the first drug against HIV.[101]

Integrase inhibitors (*raltegravir*) and fusion inhibitors/CCR5 antagonist (*maraviroc*) are new classes of drugs for the treatment of HIV and are not inhibitors or inducers of cytochrome P450, therefore they are unlikely to interact with chemotherapeutic agents.[98,102]

In an attempt to minimize chemotherapy-related complications, Gomez *et al*. adopted a number of strategies: i) use weekly chemotherapy rather than every 3 week therapy; ii) avoidance dose dense regimens; iii) the use of hormone therapy in women whose tumors are ER+ instead of chemotherapy; iv) avoidance of steroid premedication when possible and, v) the substitution *Nab-Paclitaxel* for *Paclitaxel* on occasion to avoid weekly steroid administration.[74] The liberal use of haemopoietic growth factor support (granulocyte-colony stimulating factor, G-CSF) and prophylactic fluconazole, trimethoprim/sulfamethoxazole, and acyclovir to most HIV-infected women receiving chemotherapy was also advocated.[74] In fact, a number of academics have endorsed the unrestrained use of G-CSF [41,95,102] and that all patients should be started on HAART prior to chemotherapy.[77,103]

SSA is an ideal setting in which to conduct studies exploring the DDI between HAART and chemotherapeutic drugs, because of its disproportionate burden of HIV.

BC screening in PLWHA

Lack of resources and infrastructure in the South African public healthcare system [104] and other LMIC[3] renders screening mammography (MMG) untenable.[38] Presently MMGs are performed on symptomatic and identifiable high-risk patients at specialist breast units.[104]

Current *United States Preventive Service Task Force* (USPSTF) screening guidelines recommend, for the general population, a biennial MMG for women age 50-74.[52,55] There are currently no approved guidelines or recommendations for screening WLWHA for BC [55] and most authorities believe that application of national guidelines is appropriate for WLWHA.[52,53,55] Other advocates have suggested that because WLWHA at risk of developing BC at a younger age, they should be considered for an earlier screening MMG exam than the general population.[3,8,73] As to the most appropriate way to screen WLWHA, especially those in LMIC is debatable [105,106] and beyond the scope of this article.

However, given the increase in HIV care and treatment expenditure in SSA, and increased number of PLWHA having access to clinical care and stricter medical follow up, leveraging this infrastructure to increase cancer screening and referral is a promising and likely cost-effective method to diagnose cancer at an earlier stage in PLWHA.[107] This is certainly applicable to BC awareness and screening in WLWHA[5,15,36] given the greater opportunity of patients to interact with healthcare providers.[9]

Future developments and potential areas of clinical research

HIV as a vaccine for BC

It has been established that numerous BC lines express CXCR4 receptors however do not express CD4 molecules on the cell surface. With the emergence of R5X4 and X4 HIV-1 viruses, and the fact that they kill cancer cells *in vitro*, it can be theorized that the virus can be altered to kill BC cells exclusively.

Instead of using the virus as a whole, the development of an altered virus-like particle or peptide may have the potential as a new therapy for CXCR4-related BC.[50] Since HIV-1 induces BC cell apoptosis through gp120-CXCR4 interaction, and not CD4 receptors, Endo *et al.* were able to demonstrate (*in vitro*) that a mutant of gp-120 called *E32OR*, was able to induce apoptosis BC cells but not T cells.[49] This study offers validation for the develop of a HIV-1 gp120 molecule that can treat or prevent CXCR4-BC.[108]

HAART as new chemotherapy for BC

Identification and characterization of new pharmacological activities from existing drugs represents an effective way to accelerate the translation of discoveries at the bench to the bedside.[109,110] PIs have emerged as a potential anticancer drug for several cancers[111] including BC.[109,112] *Nelfinavir* successfully inhibited the growth of HER2-positive breast cancer cells both in the lab and in mice. It seems that PIs may have the ability to cooperate with or sensitize BC to other chemotherapeutic drugs or cancer treatment options.[91]

The chemokine receptors CCR5 and CXCR4 are the co-receptors for the cellular entry of HIV-1. *Maraviroc* (CCR5 Antagonist) binds specifically and selectively to CCR5 on the surface of the CD4 cells and blocks HIV-1 binding. It conferred little or no virologic benefit in patients with X4 HIV-1 strains.[113] Microarray analysis of human BC specimens found increased expression of CCL5 and its receptor CCR5, in the basal and HER-2 genetic subtypes of BC[114] and that CCR5+ cells favor migration and invasion of these cancer cells. In *in vivo* studies, *Maraviroc* displayed anti-metastatic outcomes on basal subtype BC cell lines,[114] giving rise to the possibility of its use as therapeutic intervention or prevention of metastatic BC.[115] Results from clinical trials are keenly anticipated.[109,116]

Tamoxifen and its role in HIV treatment

Tamoxifen may serve as an antiviral agent, causing inhibition of HIV virion production, as well as preventing the spontaneous apoptosis of CD4-positive T cells and facilitating the regeneration of lymphocyte populations.[66] It was proposed as a treatment for HIV prior to the development of antiretroviral drugs[117] and recently there has been renewed interest in tamoxifen in the setting of HIV.[110]

With HAART, breast enlargement has emerged as a problem in the treatment of MLWHA. *Tamoxifen* and other anti-estrogen drugs are proving to be increasingly useful in the treatment of HAART-induced gynecomastia, after other instigates have been ruled out.[60]

The way forward

All cancer patients should be screened for HIV prior to commencement of cancer treatment as it is not uncommon to diagnose these conditions simultaneously. With an increasing incidence of BC in WLWHA, it seems plausible to screen for this malady at facilities that provide care to HIV-infected individuals and to offer them, at modicum, a clinical breast exam. Research exploring DDI between HAART and chemotherapy is urgently needed. In HIV-infected patients with cancer, adjusting the HAART regimen, to reduce toxicity and enhance efficacy of chemotherapy, should be considered. Another forethought is the permissible use of G-CSF as primary prophylaxis for myelosuppression, especially when the CD4 count is low. Repurposing antiretroviral drugs as the treatment of cancer needs to be validated in clinical trials. A significant portion of health resources in SSA countries are used for the prevention and treatment of HIV/AIDS, often at the expense of cancer services.[39] With the increasing incidence of cancer, including BC, in PLWHA and the general population, development and maintenance of oncology services is now obligatory in the region.

References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS data 2016 [Internet]. [cited 2018 May 21]. Available from: http://www.unaids.org/sites/default/files/media_asset/2016-AIDS-data_en.pdf
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS data 2017 [Internet]. 2017 [cited 2018 May 21]. Available from: http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
3. Andrade ACV de, Luz PM, Veloso VG, et al. Breast cancer in a cohort of human immunodeficiency virus (HIV)-infected women from Rio de Janeiro, Brazil: a cases series report and an incidence rate estimate. Braz J Infect Dis 2011;15:387-93.
4. McKenzie F, Zietsman A, Galukande M, et al. African Breast Cancer-Disparities in Outcomes (ABC-DO): protocol of a multicountry mobile health prospective study of breast cancer survival in sub-Saharan Africa. BMJ Open 2016;6:e011390.
5. Cubasch H, Joffe M, Hanisch R, et al. Breast cancer characteristics and HIV among 1,092 women in Soweto, South Africa. Breast Cancer Res Treat 2013;140:177-86.
6. Vorobiof DA, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. J Clin Oncol Off J Am Soc Clin Oncol 2001; 19:125S-7S.
7. Phakathi BP, Basson G, Karusseit VOL, et al. The effect of hiv infection on the surgical, chemo- and radiotherapy management of breast cancer. a prospective cohort study. Int J Surg 2016;34:109-15.
8. Reddy P, Ebrahim S, Singh B, et al. Breast Cancer and HIV: a South African perspective and a critical review of the literature. S Afr J Surg 2017;55:10-5.
9. Sarhan M, DePaz HA, Oluwole SFD. Breast cancer in women with human immunodeficiency virus infection: pathological, clinical, and prognostic implications. J Womens Health 2010;19:2261-6.
10. Widrick P, Boguniewicz A, Nazeer T, Remick SC. Breast cancer in a man with human immunodeficencey virus infection. Mayo Clin Proc 1997;72:761-4.
11. Pantanowitz L, Connolly JL. Pathology of the breast associated with HIV/AIDS. Breast J 2002;8:234-43.
12. Hamed KA, Muller KE, Nawab RA. Kaposi's sarcoma of the breast. AIDS Patient Care STDs. 2000;14:85-8.
13. Barnardt P, Narinesingh D. Primary breast lymphoma and HIV/AIDS. South Afr J HIV Med 2011;12:21.
14. Lake-lewin D, Arkel Y. Spectrum of malignancies in HIV positive individuals. Proceeding Am Soc Clin Oncol 1988;7:5.

15. Guth AA. Breast cancer and human immunodeficiency virus infection: issues for the 21st century. J Womens Health 2003;12:227-32.
16. Kiertiburanakul S, Likhitpongwit S, Ratanasiri S, Sungkanuparph S. Malignancies in HIV infected Thai patients. HIV Med 2007;8:322-3.
17. Herida M, Mary-Krause M, Kaphan R, et al. Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. J Clin Oncol Off J Am Soc Clin Oncol 2003;21:3447-53.
18. Dauby N, De Wit S, Delforge M, et al. Characteristics of non-AIDS-defining malignancies in the HAART era: a clinico-epidemiological study. J Int AIDS Soc 2011;14:16.
19. Pantanowitz L. Breast cancer and AIDS. J Natl Med Assoc 2001;93:40-1.
20. Amir H, Kaaya EE, Kwesigabo G, Kiitinya JN. Breast cancer before and during the AIDS epidemic in women and men: a study of Tanzanian Cancer Registry Data 1968 to 1996. J Natl Med Assoc 2000;92:301-5.
21. Preston-Martin S, Seaberg EC, Orenstein J, Sidawy M. Breast cancer among HIV-infected women: findings from the Women's Interagency HIV Study (WIHS). In: Proceedings of the 7th International Conference on Malignancies in AIDS and Other Immunodeficiencies [Internet]. Bethesda, Maryland; 2003 [cited 2018 May 13]. Available from: https://www.cancer.gov/about-nci/organization/oham/hiv-aids-research/oham-research/international-conference/icmaoi-2003-abs
22. Clarke CA, Glaser SL. Population-based surveillance of HIV-associated cancers: utility of cancer registry data. J Acquir Immune Defic Syndr 2004;36:1083-91.
23. Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals: AIDS. 2008;22:489-96.
24. Dal Maso L, Franceschi S, Polesel J, et al. Risk of cancer in persons with AIDS in Italy, 1985–1998. Br J Cancer 2003;89:94-100.
25. Newnham A, Harris J, Evans HS, et al. The risk of cancer in HIV-infected people in southeast England: a cohort study. Br J Cancer 2005;92:194-200.
26. Gallagher B, Wang Z, Schymura MJ, et al. Cancer incidence in New York State acquired immunodeficiency syndrome patients. Am J Epidemiol 2001;154:544-56.
27. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst 2005;97:425-32.
28. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr 2009;52:611-22.
29. Dryden-Peterson S, Medhin H, Kebabonye-Pusoentsi M, et al. Cancer Incidence following expansion of HIV treatment in Botswana. PLoS One 2015;10:e0135602.
30. Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer 2010;103:416-22.
31. Cooksley CD, Hwang L-Y, Waller DK, Ford CE. HIV-related malignancies: community-based study using linkage of cancer registry and HIV registry data. Int J STD AIDS 1999;10:795-802.
32. Serraino D, Piselli P, Busnach G, et al. Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. Eur J Cancer 2007;43:2117-23.
33. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008;123:187-94.
34. Goedert JJ, Schairer C, McNeel TS, et al. Risk of breast, ovary, and uterine corpus cancers among 85 268 women with AIDS. Br J Cancer 2006;95:642-8.
35. Krown SE. Breast cancer in the setting of HIV infection: Cause for concern? (Editorial). Cancer Invest 2002;20:590-2.
36. Guth AA. Breast cancer and HIV: What do we know? Am Surg 1999;65:209-11.
37. El-Rayes BF, Berenji K, Schuman P, Philip PA. Breast cancer in women with human immunodeficiency virus infection: implications for diagnosis and therapy. Breast Cancer Res Treat 2002;76:111-6.
38. Edge J, Buccimazza I, Cubasch H, Panieri E. The challenges of managing breast cancer in the developing world – a perspective from sub-Saharan Africa. S Afr Med J 2014;104:377-9.
39. Vanderpuye V, Grover S, Hammad N, et al. An update on the management of breast cancer in Africa. Infect Agent Cancer 2017;12:13.
40. Mody GN, Nduaguba A, Ntirenganya F, Riviello R. Characteristics and presentation of patients with breast cancer in Rwanda. Am J Surg 2013;205:409-13.
41. Voutsadakis IA, Silverman LR. Breast cancer in HIV-positive women: a report of four cases and review of the literature. Cancer Invest 2002;20:452-7.
42. Shivkumar VB, Gangane N, Sharma S, et al. Metaplastic carcinoma of the breast in an HIV-positive patient. Acta Cytol 2005;49:204-6.
43. Intra M, Gentilini O, Brenelli F, et al. Breast cancer among HIV-infected patients: the experience of the European Institute of Oncology. J Surg Oncol 2005;91:141-2.
44. Palan M, Shousha S, Krell J, Stebbing J. Breast cancer in the setting of HIV. Pathol Res Int 2011;2011:1-4.
45. Stewart T, Tsai SC, Grayson H, et al. Incidence of de-novo breast cancer in women chronically immunosuppressed after organ transplantation. Lancet Lond Engl 1995;346:796-8.
46. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370:59-67.
47. Toniolo A, Serra C, Conaldi PG, et al. Productive HIV-1 infection of normal human mammary epithelial cells. AIDS 1995;9:859-66.
48. Grover S, Martei YM, Puri P, et al. Breast cancer and HIV in Sub-Saharan Africa: a complex relationship. J Glob Oncol 2017 [Epub ahead of print].
49. Endo M, Inatsu A, Hashimoto K, et al. Human immunodeficiency virus-induced apoptosis of human breast cancer cells via CXCR4 is mediated by the viral envelope protein but does not require CD4. Curr HIV Res 2008;6:34-42.
50. Hessol NA, Napolitano LA, Smith D, et al. HIV tropism and decreased risk of breast cancer. PLoS One 2010;5:e14349.
51. Spano J-P, Lanoy E, Mounier N, et al. Breast cancer among HIV infected individuals from the ONCOVIH study, in France: Therapeutic implications. Eur J Cancer 2012;48:3335-41.
52. Oliver NT, Chiao EY. Malignancies in women with HIV Infection. Curr Opin HIV AIDS 2017;12:69-76.
53. Presti CL, Haslinger M, Wehner PB. Breast cancer in HIV-positive patients: a multi-institutional retrospective review. J Prev Med Healthc 2017;6.

54. Torres RA, Lewis W. Aging and HIV/AIDS: pathogenetic role of therapeutic side effects. Lab Invest 2014;94:120-8.
55. Aboulafia DM. Cancer screening in women living with HIV infection. Womens Health 2017;13:68-79.
56. Wani B, Aziz SA, Ganaie MA, Mir MH. Metabolic syndrome and breast cancer risk. Indian J Med Paediatr Oncol Off J Indian Soc Med Paediatr Oncol 2017;38:434-9.
57. Xue F. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr 2007;823-35.
58. Muhammad FY, Gezawa ID, Uloko A, et al. Metabolic syndrome among HIV infected patients: A comparative cross-sectional study in northwestern Nigeria. Diabetes Metab Syndr Clin Res Rev 2017;11:S523-9.
59. Ruiz M, Davis H. Breast cancer in HIV-infected patients: a retrospective single-institution study. J Int Assoc Physicians AIDS Care JIAPAC 2011;10:30-4.
60. Sikora MJ, Rae JM, Johnson MD, Desta Z. Efavirenz directly modulates estrogen receptor and induces breast cancer cell growth. HIV Med 2010;11:603-7.
61. Adefolaju GA. Effects of antiretroviral drugs on carcinogenesis in human breast and cervical cells [Internet] [Thesis]. [Johannesburg]: University of the Witwatersrand; 2015 [cited 2018 May 18]. Available from: http://wiredspace.wits.ac.za/handle/10539/17452
62. National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of AZT (CAS No. 30516-87-1) and AZT/alpha-Interferon A/D B6C3F1 Mice (Gavage Studies). Natl Toxicol Program Tech Rep Ser 1999;469:1-361.
63. Tyerman Z, Aboulafia DM. Review of screening guidelines for non-AIDS-defining malignancies: evolving issues in the era of highly active antiretroviral therapy. AIDS Rev 2012;14:3-16.
64. Retrovir (zidovudine) FDA Package Insert & Drug Facts - Iodine.com [Internet]. Iodine. [cited 2018 May 18]. Available from: https://www.iodine.com/drug/retrovir/fda-package-insert
65. Rakowicz-Szulczynska EM, Jackson B, Szulczynska AM, Smith M. Human immunodeficiency virus type 1-like DNA sequences and immunoreactive viral particles with unique association with breast cancer. Clin Diagn Lab Immunol 1998;5:645-53.
66. O-Charoenrat, P. HIV Infection and Breast cancer: two major threats to Thai women (Editorial). Siriraj Med J 2005;57:171-2.
67. Szabo S, Haislip AM, Garry RF. Of mice, cats, and men: Is human breast cancer a Zoonosis? Microsc Res Tech 2005;68:197-208.
68. Ghebre RG, Grover S, Xu MJ, et al. Cervical cancer control in HIV-infected women: Past, present and future. Gynecol Oncol Rep 2017;21:101-8.
69. Ferenczy A, Coutlée F, Franco E, Hankins C. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. CMAJ 2003;169:431-4.
70. Chirkut S. Anal human papillomavirus and anal squamous cell cancer in people living with HIV/AIDS: implications for southern Africa. South Afr J Epidemiol Infect 2014;29:12-8.
71. Rogena EA, Simbiri KO, De Falco G, et al. A review of the pattern of AIDS defining, HIV associated neoplasms and pre-malignant lesions diagnosed from 2000-2011 at Kenyatta National Hospital, Kenya. Infect Agent Cancer 2015;10:28.
72. Lanoy E, Spano J-P, Bonnet F, et al. The spectrum of malignancies in HIV-infected patients in 2006 in France: The ONCOVIH study. Int J Cancer 2011;129:467-75.
73. Calabresi A, Ferraresi A, Vavassori A, et al. Breast cancer among human immunodeficiency virus (HIV)-infected patients: the experience in Brescia, Northern Italy. Braz J Infect Dis 2012;16:396-7.
74. Gomez A, Montero AJ, Hurley J. Clinical outcomes in breast cancer patients with HIV/AIDS: a retrospective study. Breast Cancer Res Treat 2015;149:781-8.
75. Langenhoven L, Barnardt P, Neugut AI, Jacobson JS. Phenotype and treatment of breast cancer in HIV-positive and -negative women in Cape Town, South Africa. J Glob Oncol 2016;2:284-91.
76. Sseggwanyi J, Galukande M, Fualal J, Jombwe J. Prevalence of HIV/AIDS among Breast Cancer Patients and the associated Clinico-pathological features. Ann Afr Surg 2011;8:22-6.
77. Ngidi S, Magula N, Sartorius B, et al. Incidence of chemotherapy-induced neutropenia in HIV-infected and uninfected patients with breast cancer receiving neoadjuvant chemotherapy. S Afr Med J 2017;107:595-601.
78. Singh SN, Zhu Y, Chumsri S, et al. Outcomes and chemotherapy-related toxicity in HIV-infected patients with breast cancer. Clin Breast Cancer 2014;14:e53-9.
79. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. Ann Intern Med 2010;153:452-60.
80. Pantanowitz L, Sen S, Crisi GM, et al. Spectrum of breast disease encountered in HIV-positive patients at a community teaching hospital. Breast 2011;20:303-8.
81. Parameswaran L, Taur Y, Shah MK, et al. Tolerability of chemotherapy in HIV-infected women with breast cancer: are there prognostic implications? AIDS Patient Care STDs 2014;28:358-64.
82. Shaaban HS, Modi Y, Guron G. Is there an association between human immunodeficiency virus infection and breast cancer? Med Oncol 2012;29:446-7.
83. García-Tejedor A, Devesa NR, Suárez-Pumariega P, et al. Breast cancer and HIV-the adverse effects chemotherapy. Breast J 2007;13:622-3.
84. Cuvier C, Espie M, Extra JM, Marty M. Breast cancer and HIV infection: two case reports. Eur J Cancer 1997;33:507-8.
85. Oluwole SF, Ali AO, Shafaee Z, Depaz HA. Breast cancer in women with HIV/AIDS: Report of five cases with a review of the literature. J Surg Oncol 2005;89:23-7.
86. Cubasch H, Joffe M, Ruff P, et al. Breast conservation surgery versus total mastectomy among women with localized breast cancer in Soweto, South Africa. PLoS One 2017;12:e0182125.
87. Horberg MA, Hurley LB, Klein DB, et al. Surgical outcomes in human immunodeficiency virus - infected patients in the era of highly active antiretroviral therapy. Arch Surg 2006;141:1238-45.
88. Biccard BM, Madiba TE, on behalf of the South African Surgical Outcomes Study investigators. The South African Surgical Outcomes Study: A 7-day prospective observational cohort study. S Afr Med J 2015;105:465-75.
89. Housri N, Yarchoan R, Kaushal A. Radiotherapy for HIV patients: Are special precautions necessary? Cancer 2010;116:273-83.
90. Alongi F, Giaj-Levra N, Sciascia S, et al. Radiotherapy in patients with HIV: current issues and review of the literature. Lancet Oncol 2017;18:e379-93.
91. Brüning A, Friese K, Burges A, Mylonas I. Tamoxifen enhances the cytotoxic effects of nelfinavir in breast cancer cells. Breast Cancer Res 2010;12:R45.
92. Hurley J, Franco S, Gomez-Fernandez C, et al. Breast cancer

and human immunodeficiency virus: a report of 20 cases. Clin Breast Cancer 2001;2:215-20.
93. Calabresi A, Castelnuovo F, Ferraresi A, Quiros-Roldan E. Male breast cancer in an HIV-infected patient: a case report. Infez Med Riv Period Eziologia Epidemiol Diagn Clin E Ter Delle Patol Infett 2012;20:284-7.
94. Spina M, Nasti G, Simonelli C, et al. Breast cancer in a woman with HIV infection: a case report. Ann Oncol 1994;5:661-2.
95. El-Rayes BF, Berenji K, Schuman P, Philip PA. Breast cancer in women with human immunodeficiency virus infection: implications for diagnosis and therapy. Breast Cancer Res Treat 2002;76:111-6.
96. Cobucci RNO, Lima PH, de Souza PC, et al. Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: A systematic review. J Infect Public Health 2015;8:1-10.
97. Boxer L, Dale DC. Neutropenia: Causes and consequences. Semin Hematol 2002;39:75-81.
98. Pham PA, Flexner C. Emerging antiretroviral drug interactions. J Antimicrob Chemother 2011;66:235-9.
99. Max B, Sherer R. Management of the adverse effects of antiretroviral therapy and medication adherence. Clin Infect Dis 2000;30:S96-116.
100. Chow WA, Jiang C, Guan M. Anti-HIV drugs for cancer therapeutics: back to the future? Lancet Oncol 2009;10:61-71.
101. U.S. Food and Drug Administration. HIV/AIDS history of approvals - HIV/AIDS Historical Time Line 1981-1990 [Internet]. [cited 2018 May 20]. Available from: https://www.fda.gov/forpatients/illness/hivaids/history/ucm151074.htm
102. Latif N, Rana F, Guthrie T. Breast cancer and HIV in the era of highly active antiretroviral therapy: two case reports and review of the literature: breast cancer and HIV in the Era of highly active antiretroviral therapy. Breast J 2011;17:87-92.
103. Torres HA, Mulanovich V. Management of HIV infection in patients with cancer receiving chemotherapy. Clin Infect Dis 2014;59:106-14.
104. National Department of Health (South Africa). Breast cancer control policy [Internet]. Policies and Guidelines. 2017 [cited 2018 May 19]. Available from: http://www.health.gov.za/index.php/2014-08-15-12-53-24?download=2533:breast-cancer-policy
105. Yip C-H, Cazap E, Anderson BO, et al. Breast cancer management in middle-resource countries (MRCs): consensus statement from the Breast Health Global Initiative. Breast Edinb Scotl 2011;20:S12-9.
106. Galukande M, Kiguli-Malwadde E. Rethinking breast cancer screening strategies in resource-limited settings. Afr Health Sci 2010;10:89-92.
107. Menon MP, Coghill A, Mutyaba IO, et al. Association between HIV infection and cancer stage at presentation at the Uganda Cancer Institute. J Glob Oncol 2017;4:1-9.
108. Veljkovic M, Branch DR, Dopsaj V, et al. Can natural antibodies to VIP or VIP-like HIV-1 glycoprotein facilitate prevention and supportive treatment of breast cancer? Med Hypotheses 2011;77:404-8.
109. Shim JS, Rao R, Beebe K, et al. Selective inhibition of HER2-positive breast cancer cells by the HIV protease inhibitor nelfinavir. J Natl Cancer Inst 2012;djs396.
110. Butts A, Koselny K, Chabrier-Roselló Y, et al. Estrogen receptor antagonists are anti-cryptococcal agents that directly bind EF hand proteins and synergize with fluconazole in vivo. mBio 2014;5:e00765-13.
111. Toschi E, Sgadari C, Malavasi L, et al. Human immunodeficiency virus protease inhibitors reduce the growth of human tumors via a proteasome-independent block of angiogenesis and matrix metalloproteinases. Int J Cancer 2011;128:82-93.
112. Srirangam A. Effects of HIV protease inhibitor ritonavir on Akt-regulated cell proliferation in breast cancer. Clin Cancer Res 2006;12:1883-96.
113. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 Infection. N Engl J Med 2008;359:1429-41.
114. Velasco-Velázquez M, Jiao X, Fuente MDL, et al. CCR5 antagonist blocks metastasis of basal breast cancer cells. Cancer Res 2012;72:3839-50.
115. Lee E, Fertig EJ, Jin K, et al. Breast cancer cells condition lymphatic endothelial cells within pre-metastatic niches to promote metastasis. Nat Commun 2014;5:4715.
116. Halama N, Zoernig I, Berthel A, et al. Tumoral immune cell exploitation in colorectal cancer metastases can be targeted effectively by anti-CCR5 therapy in cancer patients. Cancer Cell 2016;29:587-601.
117. Laurence J, Cooke H, Sikder SK. Effect of tamoxifen on regulation of viral replication and human immunodeficiency virus (HIV) long terminal repeat-directed transcription in cells chronically infected with HIV-1. Blood 1990;75:696-703.